4-(3-Cyclopentoxy-4-[11C]methoxy-phenyl) pyrrolidin-2-one [11C]Rolipram

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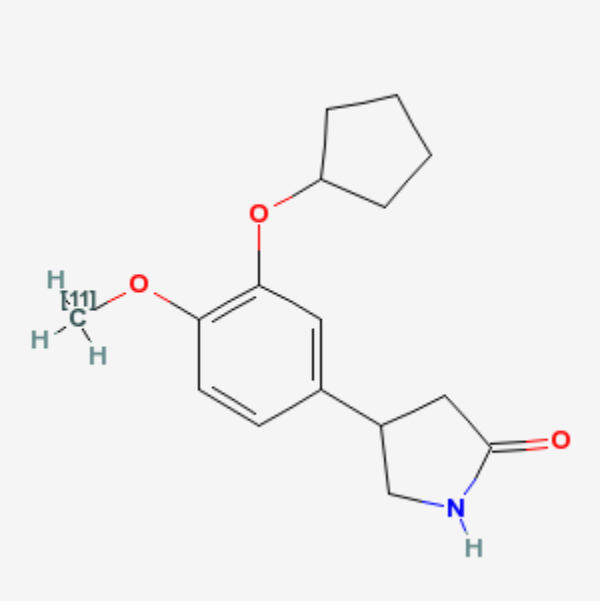
Chemical name: 4-(3-Cyclopentoxy-4-[11C] methoxy-phenyl)pyrrolidin-2-one
Abbreviated name:
Synonym: [11C]Rolipram
Backbone: Compound
Target: Phosphodiesterase type IV
Mechanism: Enzyme binding
Method of detection: PET
Source of signal: 11C
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: Yes
Non-human primate studies: Yes
Human studies: Yes



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Background

[PubMed]

Phosphodiesterases (PDEs) are composed of at least 11 families of enzymes that hydrolyze cyclic 3´,5´-adenosine monophosphate (cAMP) and/or 3´,5´-guanosine monophosphate (cGMP) to the corresponding inactive 5´-AMP and 5´-GMP, respectively (1, 2). These second-messenger cyclic nucleotides are formed in response to stimuli (such as hormones, neurotransmitters, and cytokines) to regulate cellular functions. PDEs are essential in the termination of cellular responses via their degradation of cyclic nucleotides. PDE type-4 (PDE4) is Ca^{2+}/calmodulin independent, cAMP specific, and found mainly in the kidney, brain, liver, lung, Sertoli cells, and lymphoid cells (2, 3). There are four subtypes of PDE4 enzymes. PDE4 activity and density are up-regulated by

increasing cAMP levels through phosphorylation with protein kinase A (4). PDE4 inhibitors have been studied in the treatment of neuropsychiatric disorders (depression and dementia of Alzheimer's disease) (5-7) and inflammatory diseases (asthma) (8, 9).

R/S-4-(3-Cyclopentoxy-4-methoxy-phenyl)pyrrolidin-2-one (*R*/S-rolipram) was found to be a specific inhibitor of all four subtypes of PDE4 with high affinity (K_d = 1-2 nM) (10). DaSilva et al (11). reported IC_{50} values for *R*-, *R*/*S*-, and *S*-rolipram of 2-5, 5-7, and 42-95 nM, respectively. PDE4 is highly expressed in rat brain (B_{max} >100 fmol/mg of tissue) (10, 12). The clinical program for rolipram was ultimately suspended in humans using pharmacologic doses because of its side effects, such as emesis and sedation (13). However, the action of the compound on PDE4 would be useful as a tool to better understand the biochemical basis of depression and the role that PDE4 inhibitors may play in antidepressant therapy (14). At least one study using positron emission tomography (PET) to study *R*-[^{11}C]rolipram in humans was reported in 2002. *R*-[^{11}C]Rolipram is being developed as a PET agent for the non-invasive study of PDE4 in the brain in small animals.

Synthesis

[PubMed]

Lourenco et al. (15) synthesized *R*/S-[^{11}C]rolipram as a mixture of *R* and *S* enantiomers by alkylation of the desmethyl precursor with [^{11}C]methyl iodide. Subsequent separation by high-performance liquid chromatography gave a radiochemical purity >95%. The specific activity was >14.8 GBq/μmol (>400 Ci/mmol) at time of injection. No yield was reported (15). Later, DaSilva et al. (11) described the syntheses of *S*-[^{11}C]rolipram from *S*-desmethyl-rolipram and *R*-[^{11}C]rolipram from *R*-desmethyl-rolipram with [^{11}C]methyl iodide. The ^{11}C enantiomers were prepared with a radiochemical yield of 45-75% (decay-corrected) based on [^{11}C]methyl iodide. Total synthesis time was 30 min. Radiochemical purity was >99% with specific activities of 18.5-92.5 GBq/μmol (0.5-2.5 Ci/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

R/S-[^{3}H]Rolipram binds with high affinity (K_d = 2.52 ± 0.47 nM) to sections of rat brain *in vitro* (10). Association of *R*/S-[^{3}H]rolipram to brain sections is rapid (47% of specific binding in the first minute). Dissociation of *R*/S-[^{3}H]rolipram exhibits non-first-order kinetics (three-component model; $t_{1/2}$ = 2.5 min, 50 min, and 6 h, respectively). *R*/S-[^{3}H]Rolipram binding to the brain sections was reduced by several PDE inhibitors to the level of nonspecific binding (IC_{50} = 0.9 nM for *R*-rolipram, 1.5 nM for *R*/S-rolipram, 11 nM for Ro 20-1724, and 35 nM for ICI 63.197), but not by medazepam (IC_{50} = 240 nM), diazepam (IC_{50} = 1200 nM), and IBMX (IC_{50} = 3800 nM). *In vitro* autoradiography revealed high binding site densities (in decreasing binding order) in the olfactory bulb, lateral septal nucleus, frontal cortex, subiculum, cerebellum, and hippocampus. Most of the labeled structures are part of the limbic system. Schneider et al. (16) reported previously that membrane-bound PDE4 and soluble PDE4 enzymes in rat brain homogenates exhibited K_d values of 1.2 and 2.4 nM,

respectively, and B_{max} values of 19.3 and 23.6 pmol/g tissue. The *R*-enantiomer of rolipram was 20 times more effective than the *S*-enantiomer in displacing *R*/S-[^{3}H]rolipram from the brain membranes. The authors found that the B_{max} for human cerebellar cortex membranes was ~50% that for the frontal cortex membranes. Parker et al. (17) reported a calculated affinity ratio of 8 for rat cortical membranes in *R*-[^{3}H]rolipram and *S*-[^{3}H]rolipram competition assays.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in normal rats showed high accumulation of radioactivity in the liver, followed by the brain, lung, and heart at 5 min after injection of *R*/S-[^{11}C]rolipram (15). Radioactivity from the tracer was low in the blood. *R*/S-[^{11}C]Rolipram accumulation was higher in the frontal cortex (0.57 ± 0.12% injected dose (ID)/g) and lower in the brain stem (0.26 ± 0.06% ID/g) at 45 min post injection, as predicted by the density of PDE4 enzymes. Coadministration of unlabeled *R*/S-rolipram decreased the accumulation of radioactivity in the brain regions, suggesting specific binding. Pretreatment with high doses of vinpocetine (a PDE1 inhibitor) or desipramine (a noradrenalin reuptake inhibitor) did not inhibit *R*/S-[^{11}C]rolipram accumulation in the brain regions, suggesting selectivity for PDE4 enzymes.

Fujita et al. (18) reported PET studies of the accumulation of enantiomeric [^{11}C]rolipram in the brains of normal rats, using a two-compartment model with an arterial input function for analyses. No significant differences in metabolism of the ^{11}C enantiomers were observed in blood. Both ^{11}C enantiomers remained 97% intact in the brain; however, the *R*-enantiomer was retained to a significantly greater extent than the *S*-enantiomer, and its distribution in the brain was less uniform than that of the S-enantiomer. Coadministration of unlabeled *R*-rolipram decreased the accumulation of *R*-[^{11}C]rolipram radioactivity in various brain regions to that of *S*-[^{11}C]rolipram. The average total distribution volume of all brain regions for *S*-[^{11}C]rolipram was only 14% that of *R*-[^{11}C]rolipram. The observed differences are consistent with the reported greater *in vitro* affinity of the *R*-enantiomer for PDE4 binding sites compared with the *S*-enantiomer.

Other Non-Primate Mammals

[PubMed]

Parker et al. (17) obtained PET images of the brain in pigs after injection of *R*-[^{11}C]rolipram or *S*-[^{11}C]rolipram with coadministration of either unlabeled *R*- or *S*-rolipram. In all studies, *R*-[^{11}C]rolipram exhibited a higher affinity for the PDE4 enzymes in various brain regions compared with *S*-[^{11}C]rolipram. The calculated affinity ratios from distribution volumes were 12.5 and 14.7 for *R*- and *S*-[^{11}C]rolipram, respectively. The occipital cortex exhibited the highest distribution volume, followed by the frontal cortex, thalamus, and cerebellum.

Non-Human Primates

[PubMed]

Using PET, Parker et al. (19) obtained serial brain scans in conscious monkeys after injection of *R*- or *S*-[^{11}C]rolipram with 0, 0.1, 0.3, and 1 mg/kg methamphetamine (a dopamine release inducer) pretreatment. Accumulation of radioactivity in the striata was enhanced in a dose-dependent manner corresponding to dopamine levels in striatal extracellular fluid measured with microdialysis. Administration of scopolamine,a *N*-methyl-D-aspartic acid (NMDA) receptor inhibitor), also enhanced PDE4 activity without any apparent changes in the dopamine levels. Scopolamine was reported to enhance dopamine release and reuptake simultaneously (20). The enhancements of PDE4 activity by methamphetamine and scopolamine at 1 mg/kg were abolished by preadministration of the D_1 antagonist (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-ol (SCH23390; 2 mg/kg) but not by the D_2 antagonist raclopride. Both methamphetamine and scopolamine had no effects on [^{11}C]SCH23390 [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=micad.chapter.SCH23390] striatal binding. These data suggest that dopamine in the synaptic cleft may activate D_1 receptor-coupled PDE4 activity.

Harada et al. (21) used PET to study the age-related changes in striatal dopamine D_1 receptor binding and its related PDE4 activity in the living brains of conscious young (6.4 ± 1.8 years of age) and older (19.5 ± 3.3 years of age) monkeys. [^{11}C]SCH23390 was used for quantitative analysis of D_1 receptors, and PDE4 activity, as an index of the cAMP system, was estimated by two scans with *R*- and *S*-[^{11}C]rolipram. Significant age-related decreases in D_1 receptor binding were observed in the striatum and frontal cortex. Analysis of the uptake of *R*- and *S*-[^{11}C]rolipram indicated age-related decreases in PDE4 activity, with decreases of 22.0 and 25.2% in the striatum and frontal cortex, respectively, whereas there were no significant changes in the cerebellum, which had lower accumulation than the striatum and frontal cortex. Pretreatment with the dopamine D_1 receptor antagonist SCH23390 (0.2, 0.6, and 2 mg/kg) suppressed the PDE4 activities in the striatum and frontal cortex in both age groups in a dose-dependent manner. However, suppression by SCH23390 was more pronounced in young than in older monkeys (P <0.05). These results demonstrate that the striatal PDE4 activity as well as its functional response to dopamine D_1 antagonist showed age-related impairment in the brain.

Human Studies

[PubMed]

DaSilva et al. (11) reported on PET studies in 11 healthy volunteers after injection of 370 MBq (10 mCi) of *R*-[^{11}C]rolipram. Regional brain accumulation was rapid initially and peaked at ~10 min, followed by a gradual decrease. High levels of *R*-[^{11}C]rolipram radioactivity were observed in the thalamus, which then decreased to levels similar to the binding in the cortical and striatal areas at 40 min. The peak accumulation in the thalamus corresponded to ~5% ID/L. Lower accumulation was observed in the striatum (4.5% ID/L), prefrontal cortex (4.0% ID/L), and cerebellum (3.5% ID/L). Kinetic analysis revealed that a two-tissue compartment model with arterial function input can be used to assess the brain accumulation of *R*-[^{11}C]rolipram.

Internal dosimetry data for *R*-[^{11}C]rolipram in humans are not available in the literature.

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